

## Remarks

A Request for Continued Examination accompanies this Amendment.

Claims 23-55 are pending in the application following entry of this Amendment. Claims 1-22 have been canceled. Claims 23-55 have been added. Claims 23, 50, and 54 are the only independent claims pending. For the Examiner's convenience, the following table indicates the canceled claims to which the newly added claims are believed to most closely correspond.

Approximate Claim Correspondence

Old Claim #	New Claim #	Old Claim #	New Claim #	Old Claim #	New Claim #
		9	-	17	37
1, 2	23	10	29	18	38
3	24	11	30	19	-
4	-	12	33	20	40-49
5	25	13	34	21	-
6	26	14	-	22	-
7	27	15	34, 35	-	31,50-55
8	28	16	36		

No new matter is added by the amendments and additions made herein. Support for the amendments to these claims is found in the specification as follows.

Amendments made to the paragraph bridging pages 4 and 5 of the specification merely correct obvious grammatical and spelling errors.

Each of newly added claims 23-49 is believed to be supported by at least the claims as filed, by page 3, line 17, through page 5, line 6, and by page 5, line 29, through page 7, line 14, of the specification. Claims 50-52 are supported by the structures shown atop page 8 of the specification. Claim 53 is supported by the structure of compound (1) on the top of page 9 of the specification. Claims 54 and 55 are supported by the structures of compounds (10) and (11) on page 14 of the specification.

In claim 25, decarboxylases, glucokinases, glutathionases, hexokinases, and mannosidases have been added to the claims. The Examiner had previously objected to

inclusion of these enzymes in claim 5, because claim 1 (from which claim 5 depended) recited hydrolysis and these enzymes do not catalyze hydrolysis. Claim 23 (from which claim 25 depends) does not recite hydrolysis, and so the Examiner's previous objection (Paper No. 6, page 3, first paragraph) regarding lack of antecedent basis. The Examiner had previously (Paper No. 6, page 3, second paragraph) questioned whether glutathionase is an enzyme. The Applicant respectfully contends that the enclosed entry from the Online Mendelian Inheritance in Man (OMIM) database for the disorder glutathionuria demonstrates that there is a class of enzymes known as glutathionases. Each of the enzymes added to claim 25 is disclosed in the specification at page 4, lines 17-26. The Applicant respectfully contends that the enclosed Google search engine result set (obtained using the HotBot search engine) demonstrate that "manosidase" is an obvious misspelling of the enzyme correctly spelled "mannosidase."

#### **Compliance with Previous Restriction/Election Requirements**

In the restriction / election requirement issued 16 July 2002 (Paper No. 2), the Examiner required election of a single species of enzyme. The enzyme species, 'phosphatase' was elected. Claims 23-40 and 50-54 read on this elected species.

In the restriction / election requirement issued 16 July 2002 (Paper No. 2), the Examiner required election of a single species of 'targeting molecule.' The targeting molecule species, 'antibody' was elected. Claims 23-28 and 31-55 read on this elected species.

In the restriction / election requirement issued 16 July 2002 (Paper No. 2), the Examiner required election of a single species of R<sup>1</sup> moiety. The R1 moiety species, 'gamma emitter' was elected. Claims 23-35 and 40-55 read on this elected species.

In the restriction / election requirement issued 16 July 2002 (Paper No. 2), the Examiner required election of a single species of 'BLOCK' (roughly corresponding to the "prosthetic group" recited in the presently pending claims). The BLOCK species 'phosphoric acid or sulfuric acid' was elected. Claims 23-41 and 50-54 read on this elected species.

In the restriction / election requirement issued 28 October 2002 (Paper No. 4), the Examiner required election of a single species of either 'endogenous enzyme' or 'gene therapy

induced enzyme.' The species 'endogenous enzyme' was elected. Each of claims 23-55 reads on the elected species.

In view of the restriction / election requirements and the elected species, each of claims 23-28, 31-35, 40, and 50-54 read on all elected species. Claims 29, 30, 36-39, 41-49, and 55 stand withdrawn from consideration, are believed to be subordinate to generic linking claims, and are maintained pending possible rejoinder. The Applicant believes that each of claims 23-28, 31-35, 40, and 50-54 should be examined on the merits, and that each of claims 29, 30, 36-39, 41-49, and 55 should be rejoined and examined on the merits in the event the corresponding linking claim is found to be allowable in view of the elected species.

Each of the Examiner's objections or rejections is addressed below in the order they were presented in Paper No. 36.

#### **Rejection Pursuant to 35 U.S.C. § 102(b) in View of Hansen**

The Examiner rejected claims 1, 5-15, and 17-20 pursuant to 35 U.S.C. § 102(b) in view of Hansen (U.S. Patent No. 5,851,527). In the Examiner's view (see Paper No. 6, beginning on page 3), Hansen discloses methods of treating a tumor using an enzyme-antibody complex localized to the tumor to convert a soluble prodrug to an insoluble drug which is deposited and accretes at the tumor site.

Hansen fails to disclose an enzyme "that is present in the extracellular space of the tumor and that is produced naturally by cells of the tumor" as recited in claim 23, from which claims 24-49 depend.

With regard to independent claims 50 and 54, Hansen does not disclose the structure recited in either of those claims. Hansen fails to anticipate any of claims 50-55 for that reason alone.

For the foregoing reasons, the Applicants respectfully contend that the Examiner's 35 U.S.C. § 102(b) rejection made in view of Hansen is inapplicable to each of claims 23-55, and that the rejection should be withdrawn.

### **Rejection Pursuant to 35 U.S.C. § 102(e) in View of Griffiths**

The Examiner rejected claims 1, 5-15, and 20 pursuant to 35 U.S.C. § 102(b) in view of Griffiths (U.S. Patent No. 6,361,774). In the Examiner's view (see Paper No. 6, beginning on page 4), Griffiths discloses methods of treating a tumor using an enzyme-antibody complex localized to the tumor to convert a soluble prodrug to an insoluble drug which is deposited and accretes at the tumor site.

Griffiths fails to disclose an enzyme "that is present in the extracellular space of the tumor and that is produced naturally by cells of the tumor" as recited in claim 23, from which claims 24-49 depend.

With regard to independent claims 50 and 54, Hansen does not disclose the structure recited in either of those claims. Hansen fails to anticipate any of claims 50-55 for that reason alone.

For the foregoing reasons, the Applicants respectfully contend that the Examiner's 35 U.S.C. § 102(e) rejection made in view of Griffiths is inapplicable to each of claims 23-55, and that the rejection should be withdrawn.

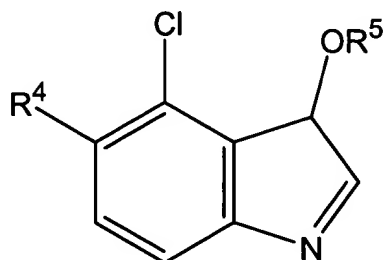
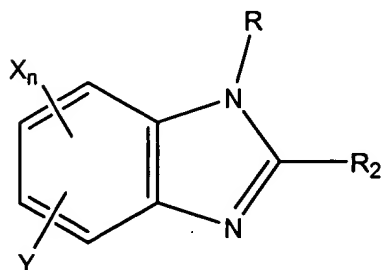
### **Rejection Pursuant to 35 U.S.C. § 103(a) Over Hansen in View of Senter, Shepard, Camden, Griffin, and Horwitz**

The Examiner rejected claims 1-3 and 5-20 over Hansen in view of one or more of Senter, Shepard, Camden, Griffin, and Horwitz.

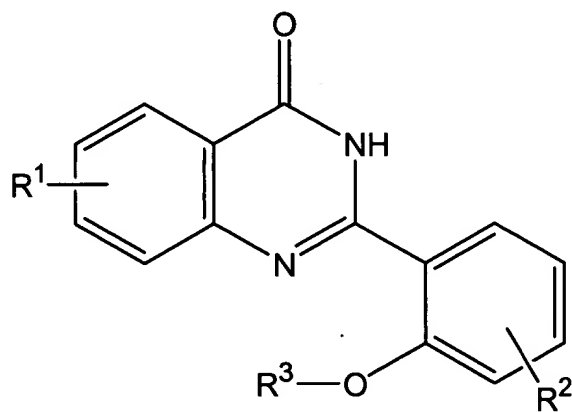
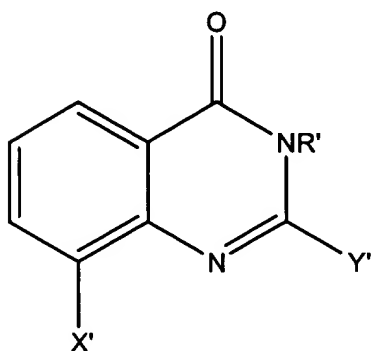
As explained above, Hansen fails to disclose an enzyme "that is present in the extracellular space of the tumor and that is produced naturally by cells of the tumor" as recited in claim 23, from which claims 24-49 depend. Similarly, none of the Senter, Shepard, Camden, Griffin, and Horwitz references discloses an enzyme "that is present in the extracellular space of the tumor and that is produced naturally by cells of the tumor" as recited in these claims.

As explained above, neither Hansen nor Griffiths discloses either of the chemical structures recited in independent claims 50 and 54. Similarly, none of the Senter, Shepard, Camden, Griffin, and Horwitz references discloses these structures, either.

Camden discloses certain benzimidazole compounds (structure below left) that differ from the structure recited in independent claim 54 (structure below right) at least in inclusion of an additional nitrogen atom in the five-membered ring.



Griffin discloses certain quinazolinone compounds (structure below left) that differ from the structure recited in independent claim 50 at least in that R<sup>1</sup> in the structure recited in claim 50 is one of a hydrogen radical, a radionuclide, and a boron cage. Griffin does not disclose that X' can be any of these moieties.



The Applicant respectfully contends that no combination of the Hansen, Griffiths, Senter, Shepard, Camden, Griffin, and Horwitz references suggest or disclose the structures recited in claims 50 and 55, and that none of these references, and no combination of them, renders obvious any of claims 50-55.

For the foregoing reasons, the Applicants respectfully contend that the Examiner's 35 U.S.C. § 103(a) over Hansen in View of Senter, Shepard, Camden, Griffin, and Horwitz is inapplicable to each of claims 23-55, and that the rejection should be withdrawn.

## Summary

For the reasons set forth above, the Applicant respectfully contends that each of claims 23-55 is in condition for allowance. Reconsideration and withdrawal of each of the Examiner's rejections are requested, and the Examiner is requested to issue a Notice of Allowance at the earliest possible time.

Respectfully submitted,

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Enclosures: Petition for a Three-Month Extension of Time  
Google search results  
OMIM Record for "glutathionuria"  
Request for Continued Examination

**OMIM**  
*Online Mendelian Inheritance in Man*



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**GLUTATHIONURIA*****Alternative titles; symbols*****GAMMA-GLUTAMYLTRANSPEPTIDASE DEFICIENCY****GGT DEFICIENCY****GGT1 DEFICIENCY****GTG DEFICIENCY****GAMMA-GLUTAMYLTRANSFERASE DEFICIENCY****GAMMA-GLUTAMYLTRANSFERASE 1, INCLUDED; GGT1, INCLUDED****GGT, INCLUDED**Gene map locus [22q11.1-q11.2](#)**TEXT**

Gamma-glutamyltranspeptidase (EC 2.3.2.2) acts as a glutathionase and catalyzes the transfer of the glutamyl moiety of glutathione to a variety of amino acids and dipeptide acceptors. This enzyme is located on the outer surface of the cell membrane. It is widely distributed in mammalian tissues involved in absorption and secretion. In humans, hepatic GGT activity is elevated in some liver diseases. GGT is released into the bloodstream after liver damage, and an elevated level of the enzyme may be a useful early sign of hepatocellular carcinoma. [Schulman et al. \(1975\)](#) described a mildly retarded adult male with glutathionemia and marked glutathionuria, whose cultured skin fibroblasts showed very low activity of the transpeptidase. Since several studies have suggested that the transpeptidase may play a role in cellular amino acid transport, the lack of aminoaciduria and aminoacidemia was noteworthy. [O'Daley \(1968\)](#) may have described the same condition. [Hammond et al. \(1995\)](#) reported sisters with GGT deficiency. The elder of the 2 sibs was detected during the course of a population screening on infants at 6 weeks of age using ascending paper chromatography of urine, which revealed a migration spot similar to that of cystine. Her growth and development were normal. During the second year, easy bruising was noted. Asthma was diagnosed at 2.5 years but was never a major problem. At 10 years of age, she began having attacks of absence and an EEG showed typical 3-Hz spike and wave activity. Seizures were controlled by valproate medication. At age 21 years, she had no significant health problems, had a good secretarial position, and was pursuing a course at technical college. The younger sister was somewhat hypotonic and inactive at birth and had a dislocated hip and mild bilateral equinovarus. Tube feeding was required for the first 4 months. Problems noted later included strabismus, easy bruising, poor coordination, and some dysmorphic features. A diagnosis of Prader-Willi syndrome (PWS; 176270) was confirmed by demonstration of an interstitial deletion of 15q11-q13. Both sisters had normal red cell glutathione and no Heinz bodies. Clearly there were no specific

clinical indicators for GGT deficiency, which in the younger sister was unrelated to PWS. 🗨

Laperche et al. (1986) cloned the structural gene for GGT from a rat kidney cDNA library. Taking advantage of its cross-hybridization with the human genome, Bulle et al. (1987) mapped the GGT gene by in situ hybridization to 22q11.1-q11.2. A minor peak was found in 22q13.1. Rouleau et al. (1988) demonstrated a PvuII polymorphism at the GGT locus and added family linkage analysis to the methods by which GGT has been assigned to chromosome 22. From studies involving restriction analysis, Heisterkamp and Groffen (1988) presented evidence that the transcribed GGT gene lies 3-prime and just distal to the BCR locus (151410). Rajpert-De Meyts et al. (1988) isolated cDNAs for GGT. Sakamuro et al. (1988) reported the primary structure of human GGT based on studies of a cDNA. The enzyme consists of 2 peptide chains, heavy and light, composed of 351 and 189 amino acids, respectively. Both are coded by a single gene; the 2 subunits of the mature enzyme are the products of processing of the single precursor peptide. The active site of GGT is located in the light subunit of the mature enzyme. A family of at least 4 GGT genes exists on chromosome 22 (Pawlak et al., 1988; Rajpert-De Meyts et al., 1988). At least 2 of these genes appear to be transcribed, since a human kidney cDNA has been isolated that differs from the placental and liver cDNAs (Pawlak et al., 1989). 🗨

Using somatic cell hybrids for hybridization with probes from a human kidney GGT cDNA clone and by amplification of a 3-prime GGT sequence by PCR, Figlewicz et al. (1993) characterized the GGT gene-pseudogene family further. They clearly mapped 3 GGT loci to chromosome 22: 2 loci (GGT1 and GGT2, 137181) between the centromere and the breakpoint cluster region (BCR; 151410) and 1 locus telomeric to BCR. In addition, they were able to identify GGT-related sequences on chromosomes 18, 19, and 20. 🗨

## REFERENCES

1. Bulle, F.; Mattei, M. G.; Siegrist, S.; Pawlak, A.; Passage, E.; Chobert, M. N.; Laperche, Y.; Guellaen, G. :  
**Assignment of the human gamma-glutamyl transferase gene to the long arm of chromosome 22.** *Hum. Genet.* 76: 283-286, 1987.  
PubMed ID : [2885259](#)
2. Figlewicz, D. A.; Delattre, O.; Guellaen, G.; Krizus, A.; Thomas, G.; Zucman, J.; Rouleau, G. A. :  
**Mapping of human gamma-glutamyl transpeptidase genes on chromosome 22 and other human autosomes.** *Genomics* 17: 299-305, 1993.  
PubMed ID : [8104871](#)
3. Hammond, J. W.; Potter, M.; Wilcken, B.; Truscott, R. :  
**Siblings with gamma-glutamyltransferase deficiency.** *J. Inherit. Metab. Dis.* 18: 82-83, 1995.  
PubMed ID : [7623451](#)
4. Heisterkamp, N.; Groffen, J. :  
**Duplication of the bcr and gamma-glutamyl transpeptidase genes.** *Nucleic Acids Res.* 16: 8045-8056, 1988.  
PubMed ID : [2901712](#)
5. Laperche, Y.; Bulle, F.; Aissani, T.; Chobert, M. N.; Aggerbeck, M.; Hanoune, J.; Guellaen, G. :  
**Molecular cloning and nucleotide sequence of rat kidney gamma-glutamyl transpeptidase cDNA.** *Proc. Nat. Acad. Sci.* 83: 937-941, 1986.



PubMed ID : [2869484](#)

6. O'Daley, S. :

**An abnormal sulphhydryl compound in urine.** (Abstract) *Irish J. Med. Sci.* 7: 578-579, 1968.

7. Pawlak, A.; Lahuna, O.; Bulle, F.; Suzuki, A.; Ferry, N.; Siegrist, S.; Chikhi, N.; Chobert, M. N.; Guellaen, G.; Laperche, Y. :

**Gamma-glutamyl transpeptidase: a single copy gene in the rat and a multigene family in the human genome.** *J. Biol. Chem.* 263: 9913-9916, 1988.

PubMed ID : [2898474](#)

8. Pawlak, A.; Wu, S.-J.; Bulle, F.; Suzuki, A.; Chikhi, N.; Ferry, N.; Baik, J.-H.; Siegrist, S.; Guellaen, G. :

**Different gamma-glutamyl transpeptidase mRNAs are expressed in human liver and kidney.** *Biochem. Biophys. Res. Commun.* 164: 912-918, 1989.

PubMed ID : [2573352](#)

9. Rajpert-De Meyts, E.; Heisterkamp, N.; Groffen, J. :

**Cloning and nucleotide sequence of human gamma-glutamyl transpeptidase.** *Proc. Nat. Acad. Sci.* 85: 8840-8844, 1988.

PubMed ID : [2904146](#)

10. Rouleau, G. A.; Bazanowski, A.; Cohen, E. H.; Guellaen, G.; Gusella, J. F. :

**Gamma-glutamyl transferase locus (GGT) displays a PvuII polymorphism.** *Nucleic Acids Res.* 16: 11848 only, 1988.

PubMed ID : [2905445](#)

11. Sakamuro, D.; Yamazoe, M.; Matsuda, Y.; Kangawa, K.; Taniguchi, N.; Matsuo, H.; Yoshikawa, H.; Ogasawara, N. :

**The primary structure of human gamma-glutamyl transpeptidase.** *Gene* 73: 1-9, 1988.

PubMed ID : [2907498](#)

12. Schulman, J. D.; Goodman, S. I.; Mace, J. W.; Patrick, A. D.; Tietze, F.; Butler, E. J. :

**Glutathionuria: inborn error of metabolism due to tissue deficiency of gamma-glutamyl transpeptidase.** *Biochem. Biophys. Res. Commun.* 65: 68-74, 1975.

PubMed ID : [238530](#)

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